20. *(Amended)* A pharmaceutical composition comprising alloactivated lymphocytes allogeneic to leukocytes in a cancer [patent] patient packaged with information for the treatment of the patient according to the method of claim 13.

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REMARKS

This paper is responsive to the Office Action dated December 17, 1999, which is the first action on the merits of the application. Claims 1-20 are pending in this application, and stand variously rejected.

Reconsideration and allowance of the application in view of the amendments and remarks made herein and the accompanying documents is respectfully requested.

Regarding amendments:

Prior reference to "Figure 1" in Example 6 has been deleted as an obvious typographical error. The text clearly refers to the treatment groups that are described in this Example, and depicted in Figures 3 and 4.

The amendments to the claims are made to correct several errors of spelling and reference pointed out in the Office Action. They are supported *inter alia* by the claims as originally filed. Applicant thanks the Examiner for an opportunity to correct these errors.

Rejection under 35 USC § 112:

Claims 9 and 15 stand rejected under 35 USC § 112 ¶ 1 as not enabled for the making or using of the invention. These claims read as follows:

> The method of claim 1 (or claim 13), wherein treatment according to the method has at least one of the following effects in at least 30% of treated subjects:
>
> a) substantial regression of the tumor in size;
>
> b) lack of recurrence of a tumor after removal; or
>
> c) decrease in rate of formation of metastasis.

The claims from which these claims depend indicate that the interval between implanting the two cell populations is at least three days.

Applicant respectfully disagrees. The application is fully enabled for the invention as claimed.

The Office Action states that "[n]either the clinical trial data on human cancer patients receiving one cytoimplant or the animal models in which received two cytoimplants indicate that at least 30% of the treated subjects displaced a substantial regression of tumor in size, a lack [of] recurrence of a tumor after removal or a decrease in rate of formation of metastases because of a lack of a disclosure within the specification on the experimental conditions."

On the contrary, Example 6 provides full details of the nature of the D74 tumor line used for study, the method of alloactivating the cells, the timing and manner in which the implant was administered, the manner in which the size of the tumor was monitored, and the manner in which animals were rechallenged. It is apparent from Figure 4 that there are at least 3 animals in the control group (Group 1), and 5 animals in treatment Groups 2, 3, and 4. Example 7 describes follow-on experiments in which treated animals that did not fully regress their tumors were then tested for resistance to further tumor challenge.

The following results were obtained:

- Three of the five animals in Group 3 completely eliminated their tumors within 17 days of the second implant (Figure 5 and Table 6). Thus, at least **60%** of the treated subjects in this group showed substantial regression of the tumor in size.
- Two of the five animals in Group 4 completely eliminated their tumors within 17 days of the second implant (Table 6). Thus, at least **40%** of the treated subjects in this group showed substantial regression of the tumor in size.
- Three of the four animals that did not eliminate their tumor, but had the tumor surgically removed, showed lack of recurrence of a tumor after removal (Table 7) — a **75%** response rate.
- Two of the four animals that had the tumor surgically removed rejected a rechallenge by the D74 tumor line (Table 7). Thus, animals were resistant to a challenge modeling tumor metastasis at a frequency of **50%** of the animals.
- At least 8 of the 10 animals in the groups treated according to the invention (Groups 3 and 4) responded by at least one of the criteria recited in claims 9 and 15 — a response rate of at least **80%**.

Claims 9 and 15 require that at least 30% of treated subjects show at least *one* of the recited effects. The observations in Examples 6 and 7 are generously above the efficacy level required in these claims.

The Office Action quotes U.S. Patent 5,837,233 (Granger) as standing for the proposition that results in animal experiments have questionable value in predicting results for humans. The section quoted is from the Background discussion of experiments reported in Redd et al. (Cancer Immunol. Immonother. 34:349, 1992), which at the time had not been implemented in human treatment. In fact, with respect to treating cancer by implanting alloactivated donor lymphocytes at the tumor site, the Granger patent shows that humans are just as responsive to the treatment (claim 1) as are experimental animals.

In fact, the Granger patent supports enablement of the invention claimed in the present application. As an issued patent, Granger is presumptively enabled for treating cancer by implanting alloactivated donor lymphocytes at the tumor site. The present application claims treating cancer or eliciting an immune response by administering two sequential doses of alloactivated donor lymphocytes at the tumor site. Preparing and administering a second treatment in a manner similar to the first treatment does not require undue experimentation, just a reapplication of established technique. Furthermore, the present application provides considerable guidance with respect to confirming that implant cells are sufficiently alloactivated (Example 3), optimizing the ratio of donor:stimulator cells (Example 4), and producing alloactivated cell compositions for commercial purposes (Example 5).

Methods for determining regression in tumor size, recurrence of a tumor, or the rate of metastases in experimental animals is exemplified in Examples 6 and 7. Determining such features in a human cancer patient are within the skill of the ordinary clinical oncologist, and will be followed as a matter of course in charting the patient's condition. For example, any oncologist knows that tumor size can be measured by such techniques as X-ray imaging, magnetic resonance imaging (MRI), CAT scan, radioisotope scintigraphy, ultrasound imaging, palpation, and caliper measurement of surgically excised and autopsy samples. Recurrence of tumor can be measured by such techniques as X-ray imaging, magnetic resonance imaging (MRI), CAT scan, radioisotope scintigraphy, ultrasound imaging, and clinical indicators of the presence of cancer, such as erythrocyte sedimentation rate (ESR). Formation of metastasis can be measured by such techniques as observation during surgical or endoscopic procedures, microscopic and immunohistochemical analysis of biopsy and autopsy samples, and clinical indicators such as ESR and Karnofsy performance score. Many of these techniques are indicated in the Detailed Description and Example 8. According to the legal standard, it is not necessary for the applicant to reiterate such procedures, since they are already known by practicing clinicians and investigators, and may be found in standard medical textbooks.

Accordingly, claims 9 and 15 are enabled by the specification as filed, and by standard knowledge of those skilled in the art.

By way of this amendment, claims 19 and 20 have been amended to correct the spelling referred to in the Office Action. Applicant is grateful to the Examiner for the opportunity to make this correction.

Withdrawal of all rejections and objections under 35 USC § 112 is respectfully requested.

Rejection under 35 USC § 103:

Claims 1-8, 10-14, and 16-20 stand rejected under 35 USC § 103(a) as being unpatentable over Granger (U.S. Patent 5,837,233) in view of Slavin et al. (U.S. Patent 5,928,639), Feldhaus et al. (U.S. Patent 5,759,805), and Haugland ("Handbook of Fluorescent Probes and Research Chemicals", Molecular Probes Inc., 1992). The Office Action states that one would be motivated to repeat administration of the pharmaceutical taught by Granger to increase the intensity of the immune response or prolong the treatment effect.

Applicant respectfully disagrees.

Two references are provided to support the contention that it would be obvious to give two doses of alloactivated donor cells. The first comes from the Granger patent, from which it is asserted that one would repeat the treatment effect described in column 4, line 4. The Granger patent does not teach or suggest the administration of a second dose. In fact, the Granger patent teaches away from the invention claimed in the present application. The cited section states:

> ". . . two patients . . . have continued to date to show a progressive reduction in tumor mass over periods of 58 and 74 weeks, respectively."
> (col. 3 line 67 to col. 4 line 4)

This indicates that one dose is sufficient to provide an anti-cancer effect for a period of more than a year. There is no indication that giving these patients a second dose would have any benefit whatsoever. Nowhere in the entire Granger patent has applicant's representative found an indication that any of the treated patients were given a second dose of alloactivated donor lymphocytes, regardless of the outcome of the first dose.

The procedures involved in administering a cell implant into the tumor of a cancer patient are both arduous and invasive — much different from taking a dose of oral medicine. For example, to administer an implant into the bed of a glioblastoma (Granger, Example 1), the skull cavity is opened, and the cells are placed near the tumor site in the brain. To administer an implant to a pancreatic cancer (Granger, Example 3), the tumor must be accessed by a surgical technique such as laparotomy, or endoscopic ultrasound-guided fine needle injection. The ethical clinician would not embark on such invasive and expensive procedures a second time, unless there was compelling motivation to do so. The Granger patent provides no such motivation.

The other reference cited in relation to multiple administrations is Slavin et al. (U.S. Patent 5,928,639. This is a very different sort of treatment administered for a very different purpose. The human subjects are patients who have undergone ablation of their normal immune response by a procedure such as whole-body chemotherapy, for treatment of what is typically a circulating cancer, such as a leukemia (Example 2). The patients can be administered autologous hematopoietic stem cells to reconstitute the immune system and provide a response against residual cancer cells, but the available autologous cells may be insufficient to treat the patient during the entire period of immune ablation.

As a substitute, the patients are given HLA-matched donor leukocytes:

> "A sample of stem cells, taken from the patient, is obtained and determined to be suitable for autologous transplantation into the patient. The sample is used to perform an autologous transplant of the patient, i.e., infusing the patient's stem cells back into the patient. The patient is then monitored until the patient is partially hematopoiesis recovered but is not fully immune-reconstituted. Then, the patient is administered an HLA-compatible, allogeneic peripheral blood leukocyte preparation having lymphocytes, in a regimen that causes a mild graft-versus-host response. (Col. 4, lines 8-18).

Upon reflecting on their animal model experiments, Slavin et al. state:

> "This implies that temporary engraftment of allogeneic effector cells may be sufficient to induce beneficial GVL [graft versus leukemia] effects against MRD [minimal residual disease], without the need for permanent residence of allogeneic effector cells, which may put the patient at risk for severe GVHD [graft versus host disease] without the need for permanent residence of allogeneic effector cells. (Col. 8, lines 47-50).

Thus, there are quite a number of important differences between the treatment in the Slavin patent, and the implant strategies described in the Granger patent and the present application:

- The administered cells in the Slavin patent are intended to have a direct "effector cell" effect against the patient's cancer. In contrast, implant therapy is believed to work not primarily by a direct cytopathic effect, but by eliciting a host immune response against the tumor (claim 13 of the present application).
- The treatment in the Slavin patent is given to patients that are immunodeficient, as a result of collateral modes of therapy, in order to provide supplementary activity. In contrast, implant therapy is typically administered to patients capable of an immune response stimulated by the administered cells and reactive against tumor antigen.

- The cells used by Slavin et al. are either autologous, or are HLA-matched with the patient as closely as possible, to prevent graft versus host disease, or premature elimination of the administered cells. In contrast, an allotypic difference is important in preparing lymphocytes for implant therapy, so that the administered cells are sufficiently alloactivated.
- Treatment according to the Slavin protocol apparently involves infusion of the cells intravenously (see *inter alia* Col. 16 line 20; Col. 17 lines 60-61; Col. 18 line 45). This is in contrast to implanting alloactivated cells at or around the site of a solid tumor, required by the Granger patent.

Obviousness can only be established by combining or modifying teachings in the cited references to produce the invention sought to be patented where there is some teaching suggestion, or motivation to do so found either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art. *In re Fine* 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones* 21 USPQ2d 1941 (Fed. Cir. 1992). Since the intent and mode of therapy is so different between the Granger and Slavin technologies, there is no motivation to combine the references in any fashion.

The subject application teaches for the first time that administering a second implant of alloactivated cells into the bed of a tumor is surprisingly effective (Detailed Description, page 10 ff.). The combined effect of two implants is much more than just additive. The second implant doesn't just slow tumor growth for a similar period as the first. The combined effect of the two implants can convey one or more of the following beneficial effects:

- A significant *decrease in tumor size*, even to the point of complete regression
- Extended survival that may be more than twice the extension conferred by a single implant
- *Ongoing* immune reactivity against the tumor, minimizing both regrowth at the primary site, and the occurrence of metastases

For these and other reasons, the invention claimed in this application represents significant progress in active immune therapies for cancer treatment.

In summary, the Granger and Slavin patents do not teach or fairly suggest the claimed invention, either alone or in combination, nor is there any motivation to combine the references. The applicant has found that administering two sequential implants of alloactivated cells into the tumor bed can have a number of surprisingly beneficial effects.

Without acquiescing the issues raised in the Office Action with respect to the other cited reference, applicant respectfully submits that the remarks made herein are sufficient to overcome the rejection under 35 USC § 103(a). Withdrawal of the rejection is respectfully requested.

Conclusion

Applicant requests that all outstanding rejections under 35 USC §§ 112 and 103 be reconsidered and withdrawn in light of the amendments and remarks made herein. The amendments and remark are believed to place the application in condition for allowance, and an early Notice of Allowance is respectfully requested.

In the event that the Examiner determines that there are other matters to be addressed, she is invited to contact applicant's representative by telephone for further discussion.

Respectfully submitted,

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